Gastric Pyloric Gland Adenoma: A Case Report, Review of Literature, and Diagnostic Challenges in the Philippine Setting

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ABSTRACT

Pyloric gland adenoma (PGA) is a rare neoplasm with definite malignant potential that is difficult to recognize because of its characteristically bland histology. We present a case of a 74-year-old female with chronic, intermittent symptoms referable to gastroesophageal reflux, bloatedness, and frequent flatus, with family history of gastric cancer. Initial endoscopy was done and biopsy revealed an inflammatory pseudopolyp. After six months, repeat endoscopy showed multiple polyps at the cardia, and biopsy of one of the visualized polyps was done. Microscopic sections of the polyp showed a neoplasm composed of discrete glands lined by simple cuboidal to columnar epithelial cells with amphophilic to eosinophilic cytoplasm without apical mucin caps, and mild nuclear atypia. Mild epithelial stratification was noted in some of the glands. PAS staining showed granular, cytoplasmic staining in tumor cells. Immunohistochemical staining with P53 showed focal, weak, nuclear staining in tumor cells. Staining with Ki67, MUC2, MUC5AC, and MUC6 was not done because the tissue had already been exhausted. The diagnosis of PGA with low-grade dysplasia has been made. The patient is apparently well, and is advised surveillance endoscopy at six-month intervals. PGA may be diagnosed in a limited resource setting, through thorough histologic examination, and use of special histochemical stains.

Key words: Pyloric gland adenoma, PS3, Ki-67, GNAT, KRAS

INTRODUCTION

Adenomatous polyps of the stomach are established precursor lesions of gastric carcinoma. The WHO classification divides such lesions as to having an intestinal or a gastric phenotype. In practice, intestinal-type adenomas are more frequently encountered; on the other hand, gastric-type adenomas are rare, and are further subdivided into foveolar or pyloric gland adenomas (PGAs).1

PGAs are rare, accounting for less than three percent of gastric polyps.2-4 The remarkably low incidence of this lesion may not necessarily be because of its rare occurrence, but may be attributed to difficulty in recognition because of the low degree of architectural disarray and cytologic atypia it usually demonstrates. In spite of its deceptively benign appearance, molecular analysis reveals that PGAs harbor several chromosomal abnormalities, as well as mutations in several oncogenes and tumor suppressor genes, which indicate that PGAs have an inherent malignant potential.5,6 To further this point, a good 30% of PGAs was found to be associated with malignant transformation;4,7 also, a few cases of PGAs are found in patients with familial adenomatous polyposis (FAP).2,6 and Lynch syndrome.2,3,6

The rarity of PGAs, and the difficulty and clinical implications of its diagnosis make this case worth reporting. In addition, to our knowledge, there has not been a formally reported case of gastric PGA in the Philippines, to date; this may be secondary to its characteristically bland histology that complicates its
recognition. Nevertheless, we attempt to document a case of gastric PGA in an elderly female with family history of gastric cancer, and to provide valuable diagnostic insights that may help practicing gastroenterologists and pathologists in a limited resource setting.

CASE

A 74-year-old female presented with chronic, intermittent, epigastric discomfort especially when lying supine, with associated frequent belching relieved with short course of proton pump inhibitors (PPIs), and non-specific gastrointestinal complaints of bloatedness and frequent flatus. Past medical history was non-contributory. Family history revealed history of gastric cancer in her father.

She sought consult with a gastroenterologist and underwent esophagogastroduodenoscopy (EGD). Multiple, pale, flat polyps were noted at the cardia; and a slightly raised polyp measuring 0.5 cm in widest dimension, was noted at the proximal body. Biopsy of the raised polyp was performed, which revealed an inflammatory pseudopapil. She underwent repeat EGD after six months for surveillance, which revealed multiple, pale, flat polyps at the cardia and fundus, and an erythematous, slightly raised polyp with reticular gastric pits, measuring 0.5 cm in widest dimension, at the cardia. The said polyp was removed and was sent to histopathology.

Microscopic examination of the polyp showed a neoplasm composed of closely packed glands lined by simple cuboidal to columnar epithelium with some glands showing mild epithelial stratification. The cells do not form apical mucin caps and exhibit mild nuclear atypia. Mitotic figures are not seen (Figure 1). Staining with Periodic Acid Schiff (PAS) showed granular, cytoplasmic staining in tumor cells (Figure 2). Immunohistochemical staining with p53 showed focal, weak, nuclear staining in tumor cells (Figure 3). Unfortunately, the tissue had been exhausted due to its diminutive size, precluding further immunohistochemical staining with Ki67, MUC2, MUC5AC, and MUC6.

Figure 1. (A) Microscopic appearance of PGA showing discrete glandular structures under the non-neoplastic foveolar epithelium (H&E, 400X); (B) Some of the glands show low-grade dysplasia with mild epithelial stratification and nuclear atypia (H&E, 400X).

Figure 2. (A) Staining with PAS showing the difference in staining pattern of the neoplastic glands and foveolar epithelium (PAS, 100X); (B) The neoplastic glands show granular, cytoplasmic staining, in contrast with that of the foveolar epithelium, which shows diffuse staining of the well-formed apical mucin caps (inset) (PAS, 400X).
Currently, the patient is apparently well, is not on any maintenance medications for her gastrointestinal complaints, and is advised close follow-up and surveillance of her gastric lesions, through EGD at six-month intervals.

**DISCUSSION**

Epidemiologically, PGAs are common in the elderly, usually in the seventh decade of life, with a slight female preponderance, which makes PGA an important differential diagnosis in elderly female patients with gastric polyps, especially when there is family history of gastric cancer, such as in our patient.

Sporadic PGAs are thought to arise in the setting of chronic mucosal injury, usually caused by *Helicobacter pylori* or autoimmune gastritis (AIG); the association between PGA and AIG partly explains the observed age and sex predilection. Between the two mentioned causes of chronic gastric injury, *H. pylori* infection is more common in our setting. In this case, *H. pylori* testing was not done, and only the lesion of interest was removed. Because of the association of sporadic PGAs with chronic mucosal injury, we therefore recommend that in cases where sporadic PGA is highly considered, biopsy of the background mucosa should also be performed aside from polypectomy, to document the presence of changes referable to chronic gastritis. One study showed that AIG is known to be associated with higher risk of high-grade dysplasia (HGD) and carcinoma. The non-association of *H. pylori* with such risk may be explained by the high prevalence of AIG in their study population. In the local setting, where *H. pylori* infection is more prevalent than AIG, when applicable or indicated, *H. pylori* testing should also be performed. Syndromic PGAs, on the other hand, generally arise from normal mucosa. In cases where the patient is young and syndromic PGA is highly considered, biopsy of the background mucosa may also be performed, but is expected to have unremarkable findings.

The clinical significance of PGA lies in its malignant potential, which it owes to certain genetic alterations. Chromosomal aberrations such as gains in 17q and 20q, and losses in 5q and 6q, have been documented in gastric PGAs; interestingly, these mutations are common in gastric adenocarcinomas. Activating *GNAS* mutations in amino acid residues 201 (R201C and R201H) and *KRAS* mutations in amino acid residues 14 (V14I) and 61 (Q61H) are considered characteristic of gastric PGAs; both mutations may be found in almost 40% of cases. *CTNNB1* mutation (S37F) has been identified in one case of gastric PGA and one esophageal PGA in one study. Recently, mutations in *SMAD4*, a tumor suppressor gene, have been initially identified in gastric PGAs; such mutations are also found in colorectal, pancreatic, and gastric carcinomas. Loss of mismatch repair (MMR) proteins has been reported in PGAs, but studies are conflicting.

PGAs pose a diagnostic challenge to pathologists mainly because of its deceptively benign histomorphology. PGAs are classically characterized by discrete, tubular structures lined by a single layer of cells with abundant amount of eosinophilic cytoplasm with ground-glass appearance, without a well-formed apical mucin cap, and basally located, round nuclei, with or without visible nucleoli. In our case, while most of the glands comprising the lesion conform to the said findings, we noted occasional foci of mild epithelial stratification and nuclear atypia; such findings point to low-grade dysplasia. The finding of dysplasia in this case makes the diagnosis of a neoplastic process more likely. Interpretation of dysplasia in PGAs is difficult because of the lack of a standardized grading scheme. Usually, authors provide operational definitions of grades of dysplasia confined within the purposes of their study. One study showed that PGAs commonly harbor dysplasia, usually of the high grade; and it assessed the degree of dysplasia based on the following classification: no dysplasia, low-grade (LGD), and HGD. Lesions with no dysplasia are composed of well-formed glands lined by a single layer of cells with basally located, round, non-atypical nuclei. Nuclear elongation and mild cytologic atypia typify LGD. Back-to-back glands with cribriforming, marked epithelial stratification, nuclear crowding, and cytologic atypia are characteristic of HGD. The said scheme is partly in congruence with that presented in the WHO classification; however, in the latter, the term ‘negative
PGAs, particularly those that do not exhibit histologic evidence of dysplasia, may be difficult to differentiate from pyloric gland hyperplasia, but it is important to do so, because the former are premalignant lesions, while the latter is a benign process. PAS stain, which highlights gastric mucin may aid in differentiating the two entities. PGAs do not form apical mucin caps, and show granular cytoplasmic staining with PAS, while non-neoplastic pyloric glands have well-formed mucin caps, and show diffuse staining of the mucin cap with PAS.7 Differentiating PGAs from foveolar-type adenomas (FTAs) poses another diagnostic difficulty, and may be of importance, because of their distinct genetic alterations that may have an impact on their biologic behavior. Compared to PGAs, FTAs are characterized by glands lined by pseudo stratified tall columnar epithelium composed of cells with well-formed apical mucin caps and elongated nuclei.6–8 While the two have distinct histomorphologic features, the possibility of hybrid differentiation and inconsistency of FTAs in forming apical mucin caps, may complicate diagnosis.1,8 Special histochemical stains, particularly PAS/ Alcian Blue stain may be of help. FTAs show strong PAS staining highlighting their mucin caps, while PGAs only show granular cytoplasmic staining.6–8 Alcian blue stains acid mucins that are typically found in the intestine, and may help identify foci of intestinal differentiation in PGAs showing mixed phenotype. Our case showed the classic PAS staining pattern of PGAs, which reinforced our diagnosis, even in the absence of the recommended immunohistochemical stains. Our findings demonstrate the use of special histochemical stains, together with meticulous histologic examination, as a viable alternative in the pathologic examination of PGAs.

Immunohistochemistry (IHC) has two main uses in the pathologic workup of PGAs: to strengthen presumptive diagnosis, and to reinforce that dysplasia is present. In terms of IHC, generally, intestinal-type adenomas express MUC2, CDX2, and CD10, and are negative for gastric mucins MUC5AC and MUC6. FTAs express MUC5AC, and are negative for MUC6 and CD10, with low CDX2 expression; while, PGAs characteristically express MUC6.1,3–8 MUC5AC expression in PGAs is variable, but in its pure pyloric gland phenotype, is limited to the foveolar surface epithelium.5,6–8 Foci of intestinal differentiation may also be encountered in PGAs, and these are positive for stains for intestinal mucins.6,9 Mixed foveolar and pyloric gland adenoma (MFPGA) may be diagnosed only with IHC using the following criteria: MUC5AC and MUC6 expression in the neoplastic glands, with 20% to more than 90% of cells being positive for MUC6. Diagnosis of MFPGA may be important, as it is found to be associated with higher risk of HGD and carcinoma in PGAs.7 These findings underscore the value of IHC, not only in differentiating PGAs from FTAs and intestinal-type adenomas, but also in diagnosing MFPGA, which has a high risk for malignant transformation.

IHC stains for P53 and Ki-67 may be used to reinforce that dysplasia is present in PGAs, in which case, patient surveillance is necessary. One study showed that degree of dysplasia in PGAs positively correlates with the magnitude of P53 and Ki-67 expression; such that lesions without histologic evidence of dysplasia show scattered, weak nuclear P53 staining, with 5-10% cells positive for Ki-67, while lesions with LGD show more intense staining than the former, with 20-35% of cells positive for Ki-67, and areas with HGD and carcinoma show more intense staining than those with LGD, with about 80% of cells positive for Ki-67.2 P53 expression in our case with LGD, matched that of lesions without histologic evidence of dysplasia; which suggests that P53 may not consistently correlate with the degree of dysplasia in PGAs. In such a case, the proliferative index may identify areas at risk for malignant transformation through increased Ki-67 expression.6 Metabolic assessment of H&E sections is central in the recognition of PGAs, and histochemical stains and IHC are necessary to support the diagnosis. While genetic testing is starting to be available in some centers in the Philippines, the cost of the test precludes its routine use in our setting.

The applicability of the recommendations presented with regard to the pathologic approach to PGAs may vary across institutions depending on the availability of the appropriate technology; the lack of additional IHC was the main weakness in the approach to this case. Nevertheless, the recognition of this neoplasm with a definite malignant potential, hiding within a deceptively benign histologic appearance, is still possible, through careful histologic examination with use of special histochemical stains, such as PAS.

CONCLUSION

PGAs should be an important differential diagnosis in elderly patients presenting with gastric polyps; particularly those with family history of gastric cancer. Management of PGA should include polypectomy with biopsy of the background gastric mucosa and H. pylori testing, especially in areas with high endemicity. Pathologic examination of PGAs should include routine histologic examination with close attention to the degree of dysplasia they harbor, and special histochemical stains such as PAS and Alcian blue stain if indicated. IHC stains for MUC5AC and MUC6 to establish diagnosis, and P53 and Ki-67 to reinforce that dysplasia is present. Pathologists should be aware that PGAs are neoplasms with definite malignant potential that intelligently hides in a deceivingly innocuous histology.

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